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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/682,332 | 10/08/2003 | David L. Shelton | 514712000600 | 8297 |

25226 7590 01/11/2007
MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

| EXAMINER | |
|---|---|
| LOCKARD, JON MCCLELLAND | |
| ART UNIT | PAPER NUMBER |
| 1647 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 01/11/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/682,332 | SHELTON ET AL. | |
| | Examiner | Art Unit | |
| | Jon M. Lockard | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application, Amendments, and/or Claims*

1. The Amendment filed 16 October 2006 has been received and entered in full. Claims 12 and 13 have been added and claims 10 and 11 remain withdrawn from consideration as drawn to a non-elected invention. Therefore, claims 1-13 are pending, and claims 1-9 and 12-13 are the subject of this Office Action.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Information Disclosure Statement*

3. The information disclosure statement (IDS) submitted on 25 September 2006 has been considered by the examiner. References 25-29 have been considered to the extent of the abstract only, as the remainder of the references are not in the English language.

### *Withdrawn Objections and/or Rejections*

4. The objections to the specification at pg 3 of the previous Office Action (mailed 16 May 2006) are withdrawn in view of the amended specification and title (filed 16 October 2006).

### *Maintained Objections and/or Rejections*

### *Claim Rejections - 35 USC § 103*

5. Claims 1-3 remain and newly added claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ro et al. (Pain. 79:265-274, 1999; cited by Applicant) in view of Zhorov et al. (U.S. Pat. No. 4,389,404). The basis for this rejection is set forth for claims 1-3 at pg 3-5 of the previous Office Action (mailed 16 May 2006).

6. Ro et al. teach administration of anti-NGF antibody for the treatment of pain following constriction injury of the sciatic nerve (See entire document), which is an art-established model of neuropathic pain.

7. The reference of Ro et al. does not teach the co-administration of NGF antibodies and an opioid analgesic, such as morphine.

8. However, the use of the opioid analgesic morphine to treat pain (including post-surgical pain) was known and was routinely used in the art at the time of the invention (See for example Zhorov et al. U.S. Pat. No. 4,389,404; particularly columns 1-2).

9. Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to co-administer antibodies to NGF and morphine because the molecules are taught individually to be effective for treating pain. *In re Kerkhoven* (205 USPQ 1069, CCPA 1980) summarizes:

> "It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a combination that is to be used for the very same purpose: the idea of combining them flows logically from their having been individually taught in the prior art."

10. The person of ordinary skill in the art would have been motivated to make the modification because treatment of pain would alleviate discomfort in the patient, and co-

administration of the antibodies to NGF would permit a lower dosage of morphine, which has well characterized side effects. The expectation of success is high as the treatment of pain with the separate administration of anti-NGF antibodies and opioid analgesics, such as morphine, are documented in the art.

11. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

12. Applicant's arguments (filed 16 October 2006) as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

13. Applicant argues at pg 8 of the response (filed 16 October 2006) that neither the cited references nor the general knowledge of one skilled in the art teach or suggest the specific combination of an anti-NGF antibody and an opioid analgesic for the treatment of pain.

14. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. In response to applicant's arguments against the references individually or the general knowledge of one skilled in the art, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As recited in the previous Office Action (mailed 16 May 2006) and reiterated at ¶10 above, one skilled in the art would have been motivated to make the modification because treatment of pain would alleviate discomfort in the patient, and co-administration of the antibodies to NGF would permit a lower dosage of morphine, which has

well characterized side effects. The expectation of success is high as the treatment of pain with the separate administration of anti-NGF antibodies and opioid analgesics, such as morphine, are documented in the art.

15. Applicant argues at pg 8-10 of the response (filed 16 October 2006) that one skilled in the art would not have a reasonable expectation of success, i.e., the expectation that an anti-NGF antibody and an opioid analgesic when used in conjunction would provide enhanced pain treatment or allow a reduced dosage of opioid to effect the same amount of pain reduction. In support of this argument, Applicant cites Sunshine et al., which demonstrates that the combination of aspirin and codeine provides no additive effect in pain treatment as compared to aspirin alone.

16. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. In response to applicant's argument that the references fail to show certain features of applicant's invention, i.e., that an anti-NGF antibody and an opioid analgesic, when used in conjunction, allows a reduced dosage of an opioid analgesic to effect the same amount of pain reduction, it is noted that the features upon which Applicant relies (i.e., reduced dosage of opioid analgesic) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

17. Regarding the argument that Example 1 demonstrates that treatment with anti-NGF antibody Mab 911 in conjunction with the opioid analgesic morphine was more effective in reducing resting pain than treatment with morphine alone or with the antibody alone, thus

indicating that the combination treatment is additive in pain reduction, it is noted that additivity of compounds, or even synergism of compounds, is not *per se* unexpected. The showing should demonstrate that synergism is unexpected. See *In re* Huellmantel, 324 F.2d 998, 139 USPQ 496 (CCPA 1963); *In re* Meinhardt, 392 F.2d 273, 157 USPQ 270 (CCPA 1968). In the instant case, one skilled in the art would expect that conjunctive administration of anti-NGF antibodies and morphine would be more effective at relieving pain than either the antibody or morphine alone, since the mechanism of action is different for each of the compounds, and both have been shown to be effective pain relievers.

18. The Sunshine et al. reference is not sufficient to establish that additivity or synergism in pain relief is unexpected. First, it is noted that the proper standard is that a person of ordinary skill in the art would have a reasonable expectation of success that the combination therapy (anti-NGF antibody and morphine) would be effective, there need not be a guarantee that either an additive or synergistic effect would occur. While Sunshine et al. report that there was no difference in efficacy between aspirin alone and aspirin plus codeine in the treatment of pain, the design of the study was to compare suprofen to other types of pain relief, including suprofen vs. aspirin vs. aspirin plus codeine. Therefore, the facts of Sunshine et al. are distinguished from the facts of the instant application since the claims are drawn to methods of treating pain by co-administering an anti-NGF antibody with and opioid analgesic. Moreover, another study by Sunshine et al. (Clin. Pharmacol. Ther. 42:374-380, 1987) teaches that ibuprofen and codeine in combination are more efficacious than either ibuprofen or codeine alone. For a review of synergism between analgesics, see Kehlet (Ann. Med. 27:259-262, 1995), who describes combination analgesic therapy as "rational" (see for example, abstract, pg 259, and pg 260).

Therefore, although not every combination of analgesic provides additive or synergistic effects, it is the state of the art that many combinations do provide greater relief. Thus, one of ordinary skill in the art would reasonably expect success in treating pain through a combination of compounds that have been shown individually to be effective at treating pain.

19. Claims 1-7 remain and newly added claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ro et al. (Pain. 79:265-274, 1999; cited by Applicant) in view of Zhorov et al. (U.S. Pat. No. 4,389,404) as applied to claims 1-3 above, and further in view of Hongo et al. (Hybridoma. 19(3):215-27, 2000; cited by Applicant) and Hoogenboom et al. (WO 93/06213; cited by Applicant). The basis for this rejection is set forth for claims 1-7 at pg 5-6 of the previous Office Action (mailed 16 May 2006).

20. The teachings of Ro et al. and Zhorov et al. are set forth above. Ro et al. and Zhorov et al. do not teach anti-NGF antibodies that bind human NGF, antibodies that bind human NGF with a binding affinity of about 10nM or less than about 10nM. Ro et al. and Zhorov et al. also do not teach human NGF antibodies or humanized NGF antibodies.

21. However, such antibodies as well as methods of making them were known in the art at the time of the invention. Hongo et al. teach humanized antibodies that bind human NGF with a binding affinity of about 10nM or less than 10nM (See pg 217, Table 1). Furthermore, Hoogenboom teach how to make human antibodies (See entire document).

22. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Ro et al. and Zhorov et al. by using the antibodies taught by Hongo et al. and Hoogenboom et al. because humanized and human antibodies offer the

advantage of being more specific for humans and less likely to produce allergic or immune complex sensitivity. (See Hoogenboom et al., pg 1, lines 1-22). The motivation to do so is also provided by Hoogenboom et al. who teach that human or humanized antibodies reduce the likelihood of inappropriate immune responses that interfere with therapy (See pg 1, lines 1-22). The person of ordinary skill in the art would have a reasonable expectation of success because the human or humanized antibodies would likely perform better for the reasons set forth above.

23. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

24. Applicant's arguments (filed 16 October 2006) as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

25. Applicant argues at pg 11-12 of the response (filed 16 October 2006) that, as previously discussed, neither Ro et al. nor Zhorov et al. teach or suggest that administration of an anti-NGF antibody in conjunction with an opioid analgesic provides additive pain relief; and one skilled in the art would not have had a reasonable expectation that this additive effect in pain relief could be achieved by the claimed combination treatment. Applicant further argues that neither Hongo et al. nor Hoogenbom et al. provide any additional suggestions for the combination treatment as claimed.

26. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re*

*Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). One skilled in the art would have been motivated to make the modification because treatment of pain would alleviate discomfort in the patient; co-administration of the antibodies to NGF would permit a lower dosage of morphine, which has well characterized side effects; and human or humanized antibodies reduce the likelihood of inappropriate immune responses that interfere with therapy (See ¶22 *supra*). The expectation of success is high as the treatment of pain with the separate administration of anti-NGF antibodies and opioid analgesics, such as morphine, are documented in the art, and humanized and human antibodies offer the advantage of being more specific for humans and less likely to produce allergic or immune complex sensitivity.

27. Furthermore, as previously stated, additivity of compounds, or even synergism of compounds, is not *per se* unexpected. The showing should demonstrate that synergism is unexpected. See *In re* Huellmantel, 324 F.2d 998, 139 USPQ 496 (CCPA 1963); *In re* Meinhardt, 392 F.2d 273, 157 USPQ 270 (CCPA 1968). Accordingly, the issues raised by the Examiner concerning the arguments against Ro et al. and Zhorov et al. at ¶16-18 *supra* are directly applicable here.

28. Claims 1-3, 8, and newly added claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ro et al. (Pain. 79:265-274, 1999; cited by Applicant) in view of Zhorov et al. (U.S. Pat. No. 4,389,404) as applied to claims 1-3 above, and further in view of McMahon et al. (Nature Medicine. 1(8):774-780, 1995; cited by Applicant), and Brennan, T.J. (ILAR. 40(3):129-136, 1999).

29. Ro et al. teach administration of an anti-NGF antibody for the treatment of pain following constriction injury of the sciatic nerve (See entire document), which simulates a nerve injury and is an art-established model of neuropathic pain.

30. Neither the reference of Ro et al. nor Zhorov et al. teach the co-administration of antibodies to NGF and morphine for the treatment of post-surgical pain.

31. McMahon et al. teach that neutralization of endogenous NGF with trkA-IgG prevents hyperalgesia in a carrageenan-induced model of inflammation (See entire document).

32. Brennan teaches that the mechanisms for initiation and maintenance of pain after incision likely involve a combination of nerve injury, inflammation, pH changes, and central nervous system plasticity (See pg 133).

33. Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to co-administer the anti-NGF antibodies taught by Ro et al. and the morphine taught by Zhorov et al. for the treatment of post-surgical pain.

34. The person of ordinary skill in the art would have been motivated to use the antibodies taught by Ro et al. and the morphine taught by Zhorov et al. to treat post-surgical pain because surgery is known to cause pain and it is obvious to treat the pain to alleviate discomfort in the patient.

35. The expectation of success is high since neutralizing endogenous NGF with an anti-NGF antibody has been shown to alleviate hyperalgesia in a nerve injury model as taught by Ro et al., neutralizing endogenous NGF with trkA-IgG immunoadhesion has been shown to alleviate hyperalgesia in a model of inflammation as taught by McMahon et al., and both nerve injury and inflammation are components of incisional (i.e., post-operative) pain as taught by Brennan.

36. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

37. Claims 1-7, 9, and newly added claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ro et al. (Pain. 79:265-274, 1999; cited by Applicant) in view of Zhorov et al. (U.S. Pat. No. 4,389,404), McMahon et al. (Nature Medicine. 1(8):774-780, 1995; cited by Applicant), and Brennan, T.J. (ILAR. 40(3):129-136, 1999) as applied to claims 1-7 above, and further in view of Hongo et al. (Hybridoma. 19(3):215-227, 2000; cited by Applicant) and Hoogenboom et al. (WO 93/06213, cited by Applicant).

38. The teachings of Ro et al., Zhorov et al., Bennett et al., McMahon et al., and Brennan are set forth above. None of the references teach anti-NGF antibodies that bind human NGF, antibodies that bind human NGF with a binding affinity of about 0.1 nM or less than about 0.1 nM. The references also do not teach human NGF antibodies or humanized NGF antibodies.

39. However, such antibodies as well as methods of making them were known in the art at the time of the invention. Hongo et al. teach humanized antibodies that bind human NGF with a binding affinity of about 0.1nM or less than about 0.1 nM (See pg 217, Table 1). Furthermore, Hoogenboom et al. teach how to make human antibodies (See entire document).

40. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Ro et al., Zhorov et al., and McMahon et al., and Brennan as set forth above by using the antibodies taught by Hongo et al. and Hoogenboom et al. because humanized and human antibodies off the advantage of being more specific for humans and less likely to produce allergic or immune complex sensitivity (See Hoogenboom et al., pg 1, lines 1-

22). The motivation to do so is also provided by Hoogenboom et al. who teach that human or humanized antibodies reduce the likelihood of inappropriate immune responses that interfere with therapy (See pg 1, lines 1-22). The person of ordinary skill in the art would have a reasonable expectation of success because the human or humanized antibodies would likely perform better for the reasons set forth above.

41. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

***Double Patenting***

42. Claims 1-9 remain and newly added claims 12 and 13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 9-10 of copending Application No. 10/783,730 (US 2004/0253244 A1) in view of Breault et al. (U.S. Pat. No. 5,843,942) for reasons of record as set forth at pg 7-8 of the previous Office action (mailed 16 May 2006).

43. Applicant's intention to resolve the issue is noted. However, it is noted that deferral of arguments until after the claims have been found otherwise allowable will not be considered timely. Accordingly, the provisional rejection is maintained.

44. Claims 1-9 remain and newly added claims 12 and 13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4-7 of copending Application No. 10/682,638 in view of Zhorov et al. (U.S. Pat. No.

4,389,404) for reasons of record as set forth at pg 8-9 of the previous Office action (mailed 16 May 2006).

45. Applicant's intention to resolve the issue is noted. However, it is noted that deferral of arguments until after the claims have been found otherwise allowable will not be considered timely. Accordingly, the provisional rejection is maintained.

46. Claims 1-4, and 7 remain and newly added claims 12 and 13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 6 of copending Application No. 10/791,162 in view of Zhorov et al. (U.S. Pat. No. 4,389,404) for reasons of record as set forth at pg 10-11 of the previous Office action (mailed 16 May 2006).

47. Applicant's intention to resolve the issue is noted. However, it is noted that deferral of arguments until after the claims have been found otherwise allowable will not be considered timely. Accordingly, the provisional rejection is maintained.

48. Claims 1-4 and 7 remain and newly added claims 12 and 13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20, 22, 36, and 37 of copending Application No. 11/104,248 in view of Zhorov et al. (U.S. Pat. No. 4,389,404) for reasons of record as set forth at pg 11-12 of the previous Office action (mailed 16 May 2006).

49. Applicant's intention to resolve the issue is noted. However, it is noted that deferral of arguments until after the claims have been found otherwise allowable will not be considered timely. Accordingly, the provisional rejection is maintained.

50. Claims 1-4 and 6-7 remain and newly added claims 12 and 13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10, and 12-14 of copending Application No. 11/102,201 for reasons of record as set forth at pg 12-13 of the previous Office action (mailed 16 May 2006).

51. Applicant's intention to resolve the issue is noted. However, it is noted that deferral of arguments until after the claims have been found otherwise allowable will not be considered timely. Accordingly, the provisional rejection is maintained.

***Summary***

52. No claim is allowed.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 7:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback**, can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Jon M. Lockard, Ph.D.
January 4, 2007

**CHRISTINE J. SAOUD**
**PRIMARY EXAMINER**
Christine J. Saoud